

# NAFLD and NASH: A Growing Problem in Adults and Adolescents

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# Overview

- Epidemiology and Natural History of NAFLD.
- Current Challenges:
  - NAFLD is not a serious disease in young patients
  - There is no FDA-approved treatment for NAFLD
- Discuss the management of NAFLD today.

# NAFLD is the Hepatic Manifestation of Obesity/IR



## Metabolic Syndrome

- Insulin Resistance/ DM2
- Dyslipidemia
- Hypertension

## NAFLD

- Elevated ALT
- Fatty liver on US

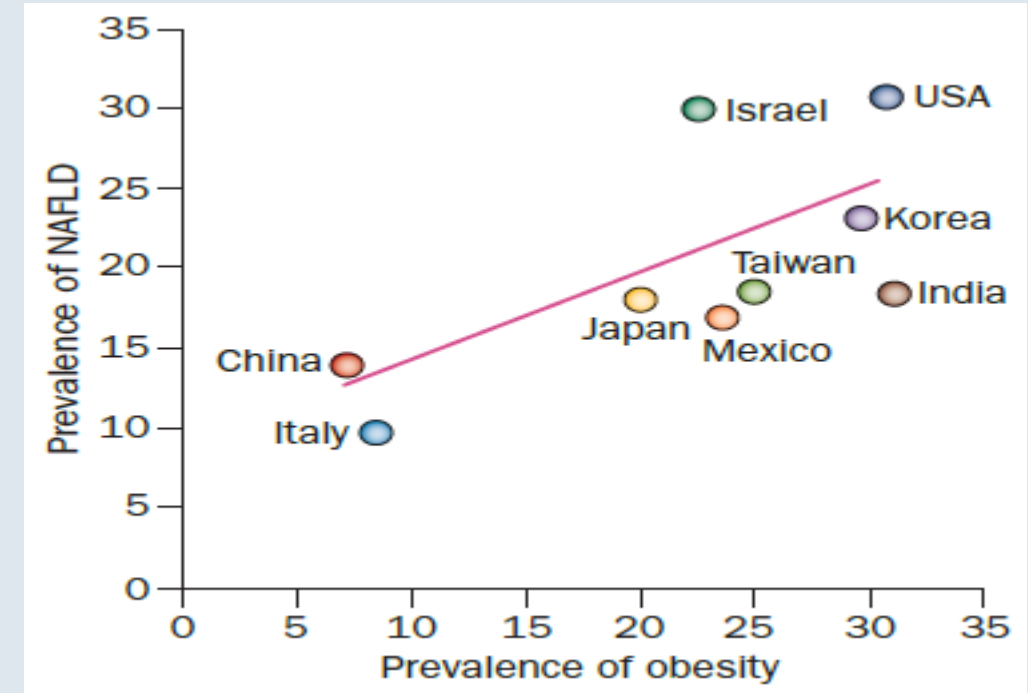
# NAFLD Prevalence

- **Adults**

- Overall: ~ 30%
- Obese: ~ 50-70%
- Severely Obese: 85%
- DM2: ~ 65-75%

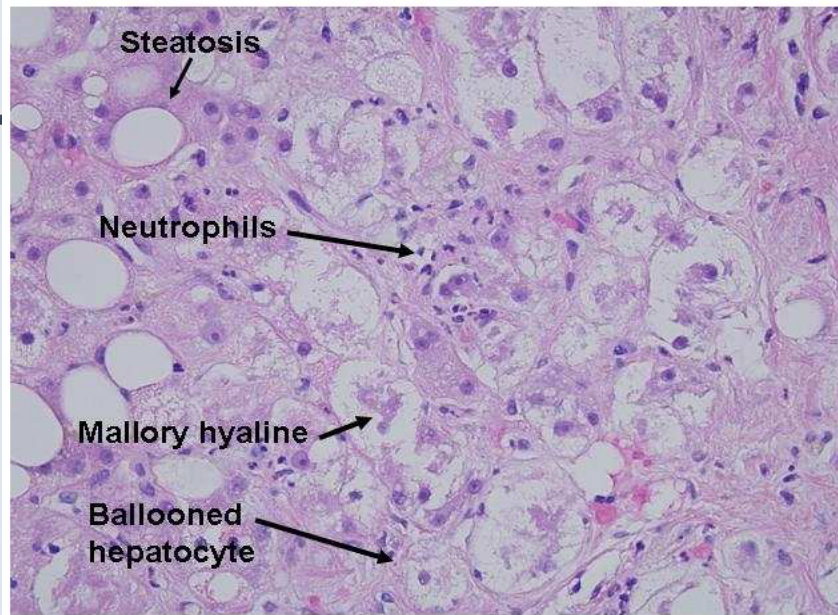
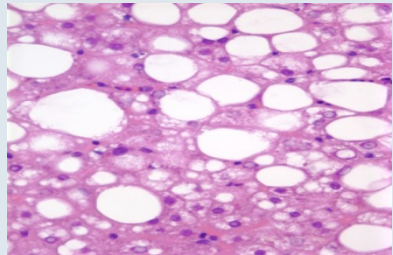
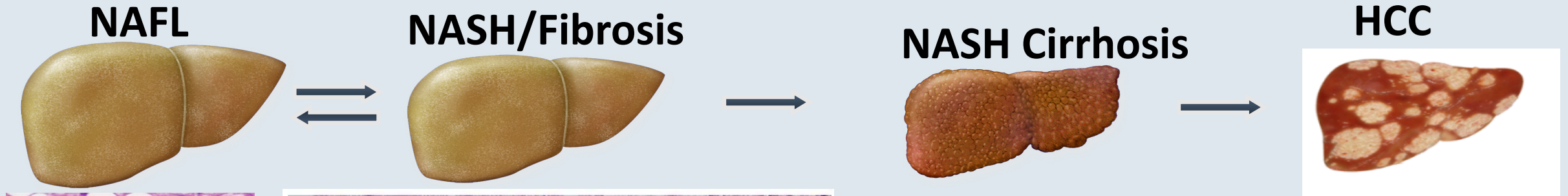
- **Children**

- Overall: ~ 10%
- 15-19 years: ~ 17%
- Obese: ~ 50%





# The NAFLD Spectrum



**80-100  
Million**

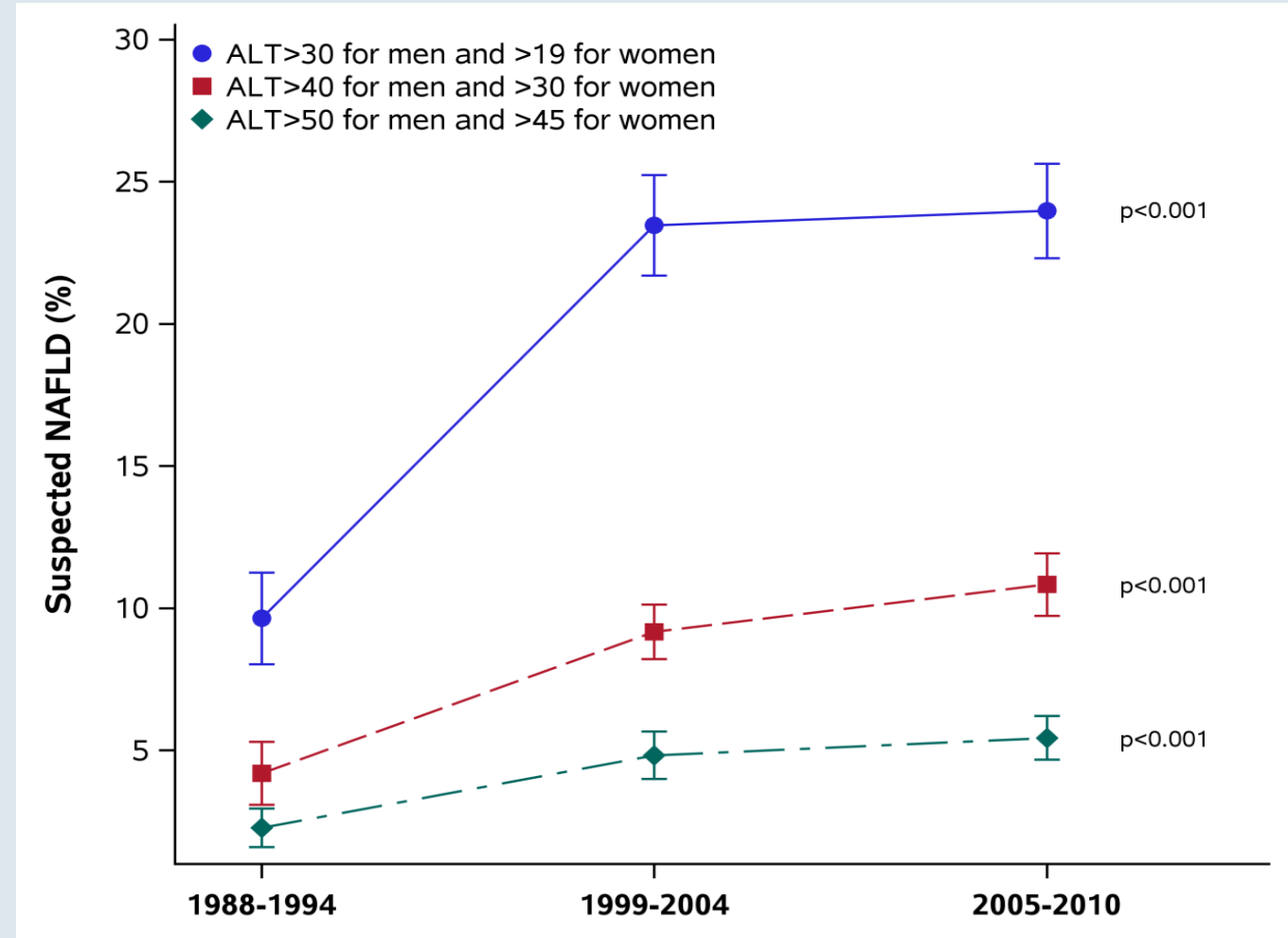
NAFLD Activity Score	
Steatosis (0-3)	
5-33%	1
34-65%	2
≥66%	3
Inflammation (0-3)	
<2 under 20x	1
2-4 under 20x	2
>4 under 20x	3
Ballooning (0-2)	
Few	1
Many	2

# Challenge 1

NAFLD is not a serious disease in young patients

# Burden of NAFLD Among Young Adults in the US

- National Health and Examination Survey (NHANES) database
- 14,371 subjects
- Age 18-35
- Three study periods:
  - 1988-1994
  - 1999-2004
  - 2005-2010



# Young Kids, Old Bodies

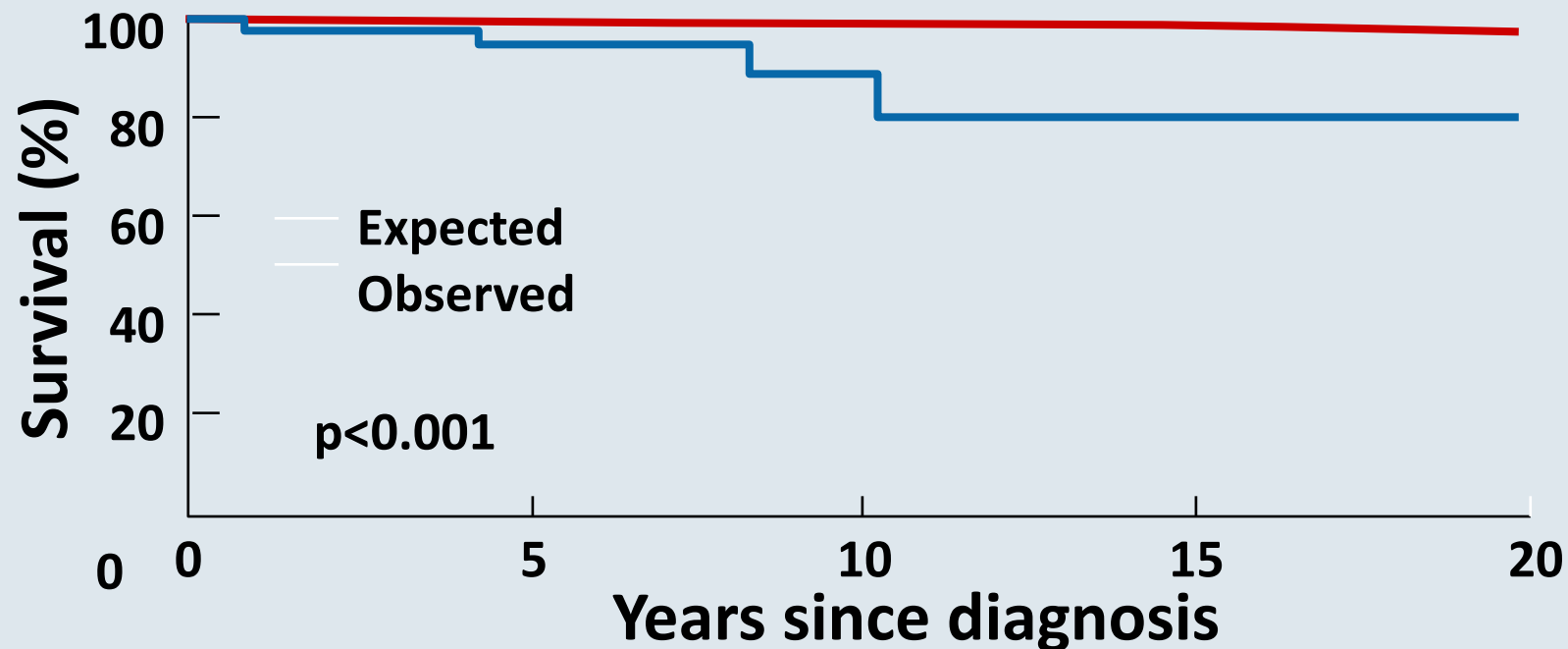


**Obesity is turning a generation of children into biological adults, ageing them before their time**

# Natural History of NAFLD in Children

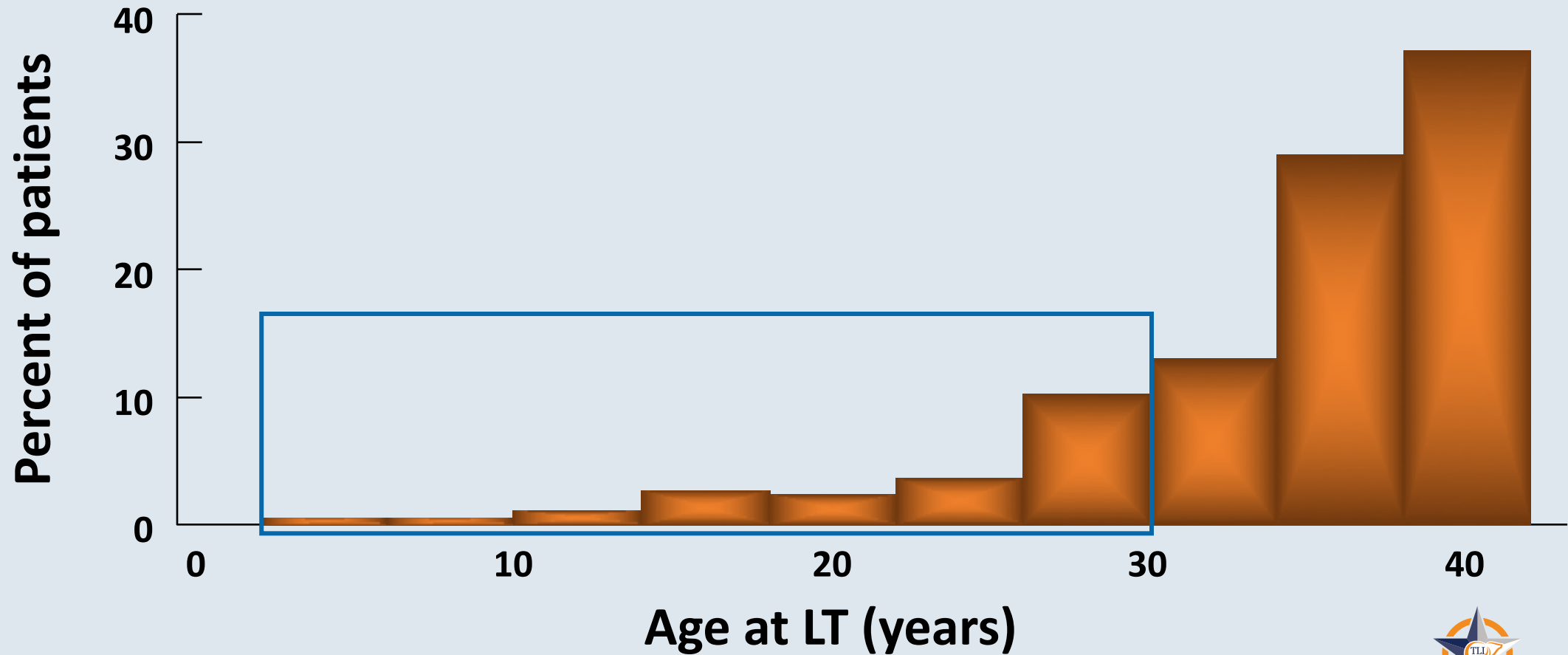
## A hospital-based cohort study

n = 66 children with NAFLD, follow up for up to 20 years



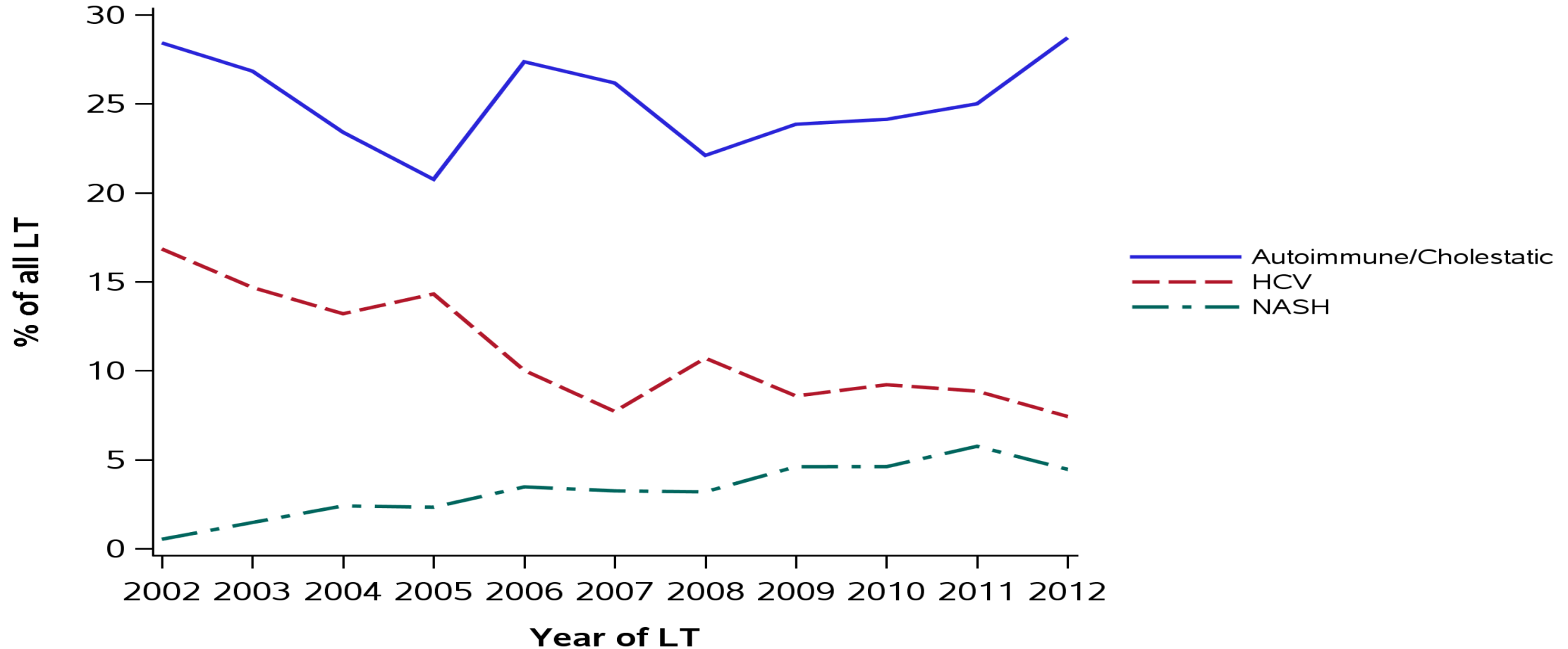
2 patients developed NASH-cirrhosis that required LT at 20 and 25 years

# LT for NASH in Children and Young Adults





# NASH is the most rapidly increasing indication for OLT in young adults



# Challenge 2

There is no FDA-approved treatment for  
NAFLD



# The Race to Cure NASH: Four Medications in Phase III RTCS

- **Obeticholic acid (OCA):** FXR agonist (REGENERATE)
- **Cenicriviroc:** CCR2/ CCR5 inhibitor (STELLARIS)
- **Selonsertib:** Apoptosis signal-regulating kinase (ASK1) inhibitor (STELLAR-3 and -4)
- **Elafibranor:** PPAR  $\alpha$ - $\delta$  agonist (RESOLVE IT)

# Case Presentation

- A 55-year-old male with obesity (BMI of 40 kg/m<sup>2</sup>) presents to you with abnormal LFTs x 6 months.
- ALT 118 U/L, AST 106 U/L, with normal bilirubin, alkaline phosphatase and INR.
- On physical exam you notice mild hepatomegaly.
- Liver US showed diffuse increase in echogenicity and vascular blurring consistent with fatty infiltration. You suspect NAFLD.

# How Do I Manage My Patient with NAFLD

1. Rule out other etiologies of elevated ALT or fatty infiltration of the liver.
2. Assess for co-morbidities (DM2, HTN, Dyslipidemia, OSA).
3. Assess Severity (NASH, advanced fibrosis)
4. Treatment:
  - Lifestyle
  - Pharmacologic

# Laboratory Assessment for NAFLD

## Chronic Liver Disease Panel

- ☐ CBC + AUTO DIFF  
Lab, Routine, BLOOD
- ☐ HEPATIC FUNCTION PNL  
Lab, Routine, BLOOD
- ☐ GGT BLD  
Lab, Routine, BLOOD
- ☐ BASIC METABOLIC PNL  
Lab, Routine, BLOOD
- ☐ LIPID PANEL BASIC  
Lab, Routine
- ☐ PROTHROMBIN TIME/PT  
Lab, Routine, BLOOD
- ☐ HEP REMOTE PANEL BL  
Lab, Routine, BLOOD
- ☐ HEP A AB TOTAL  
Lab, Routine, BLOOD
- ☐ ANA BLOOD  
Lab, Routine, BLOOD
- ☐ SMOOTH MUSCLE AB PNL SCRNL  
Lab, Routine, BLOOD
- ☐ LKM AB  
Lab, Routine, BLOOD
- ☐ ALPHA-1-ANTITRYPS BL  
Lab, Routine, BLOOD
- ☐ IRON + TIBC  
Lab, Routine, BLOOD
- ☐ FERRITIN BLD  
Lab, Routine, BLOOD
- ☐ CERULOPLASMIN BLD  
Lab, Routine, BLOOD
- ☐ CELIAC SCREEN WITH REFLEX  
Lab, Routine, BLOOD
- ☐ CK CREATINE KINASE  
Lab, Routine, BLOOD

## NASH Panel

- ☐ CBC + AUTO DIFF  
Lab, Routine, BLOOD
- ☐ HEPATIC FUNCTION PNL  
Lab, Routine, BLOOD
- ☐ GGT BLD  
Lab, Routine, BLOOD
- ☐ BASIC METABOLIC PNL  
Lab, Routine, BLOOD
- ☐ LIPID PANEL BASIC  
Lab, Routine
- ☐ TSH BLD  
Lab, Routine, BLOOD
- ☐ HGB A1C  
Lab, Routine, BLOOD
- ☐ INSULIN ASSAY BLOOD  
Lab, Routine, BLOOD
- ☐ GLUCOSE FASTING BLD  
Lab, Routine, BLOOD
- ☐ C-REACTIVE ULTRA SEN  
Lab, Routine, BLOOD
- ☐ LIPOPROTEIN (A)  
Lab, Routine, BLOOD
- ☐ ALBUMIN RANDOM URINE  
Lab, Routine, URINE
- ☐ VITAMIN D 25 HYDROXY  
Lab, Routine, BLOOD

# Assessment of the Severity of NAFLD

## NAFLD fibrosis score Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**  
*A noninvasive system that identifies liver fibrosis in patients with NAFLD*  
Hepatology 2007;45(4):846-854 [doi:10.1002/hep.21496](https://doi.org/10.1002/hep.21496)

Age (years)

BMI (kg/m<sup>2</sup>)

IGF/diabetes ☐

AST

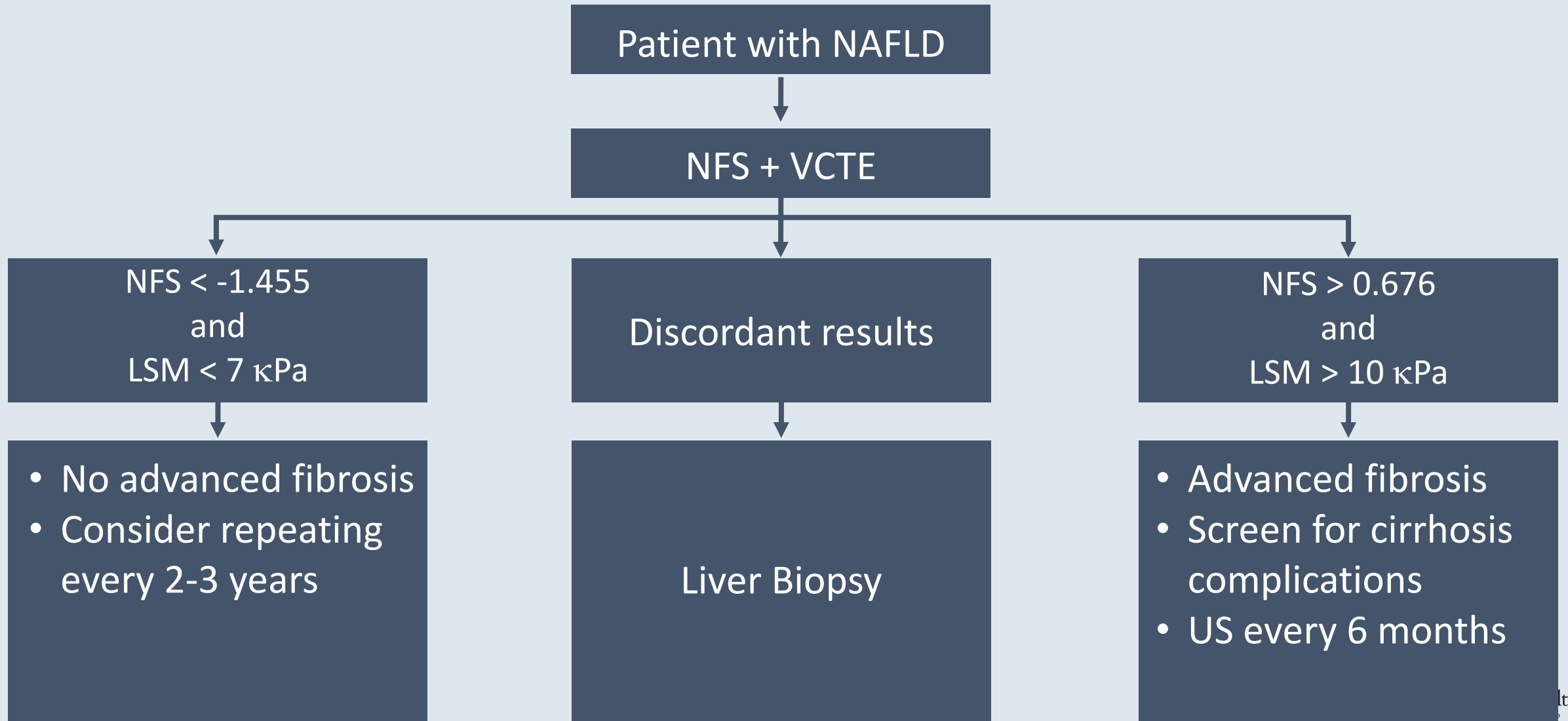
ALT

Platelets (×10<sup>9</sup>/l)

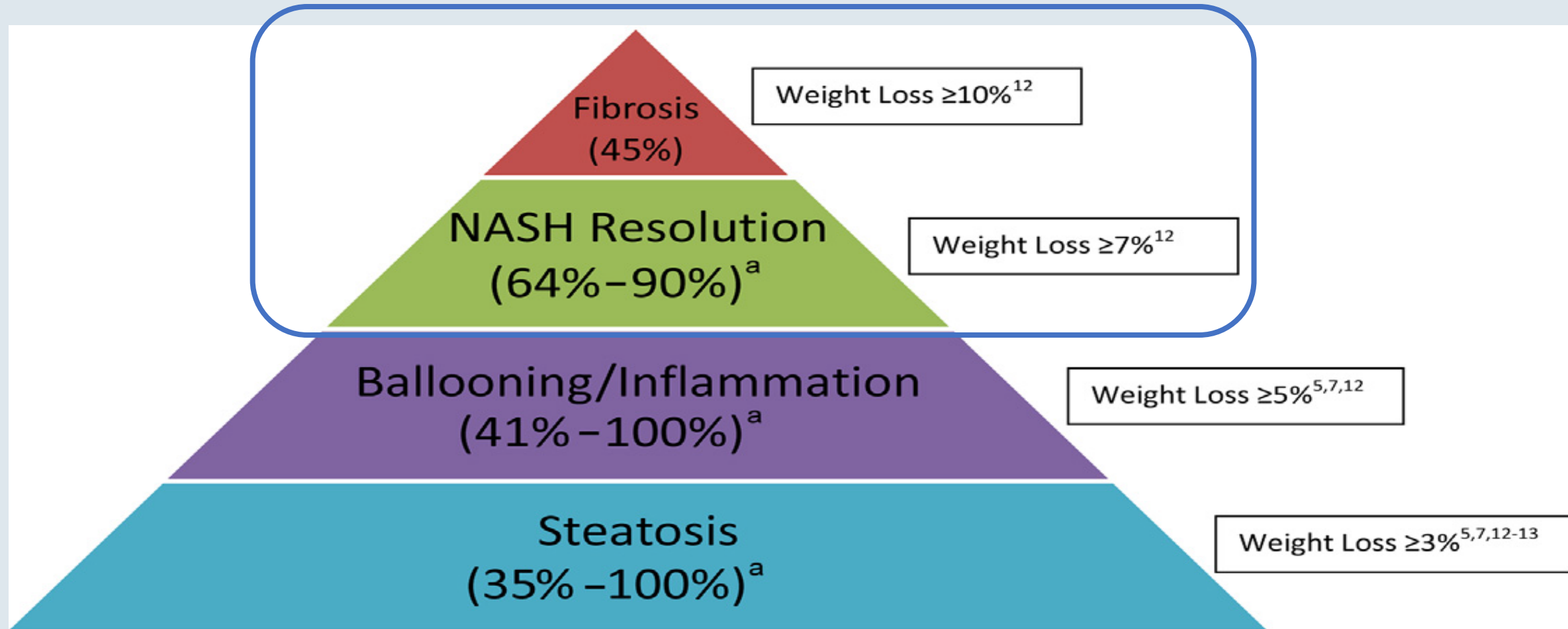
Albumin (g/l)



# Algorithm for Assessing the Severity of NAFLD



# Treatment: % Weight Loss Associated With Histological Improvement





# The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease

HIGH IN:



MUFA

PUFA

Folate

Fiber

Antioxidants

LOW IN:



Saturated  
Fat



N = 12

6 wk diet MD/LFD

6 wk washout

6 wk diet MD/LFD

Baseline  
testing

End-of-study  
testing

Baseline  
testing

End-of-study  
testing

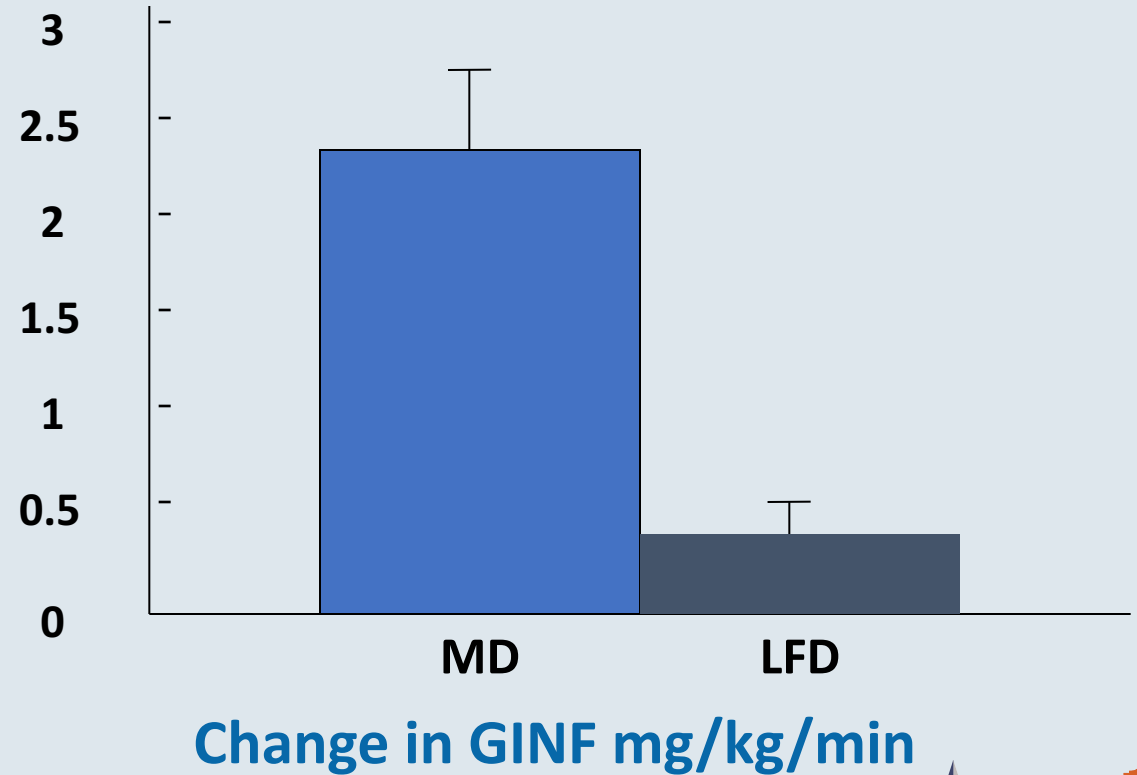
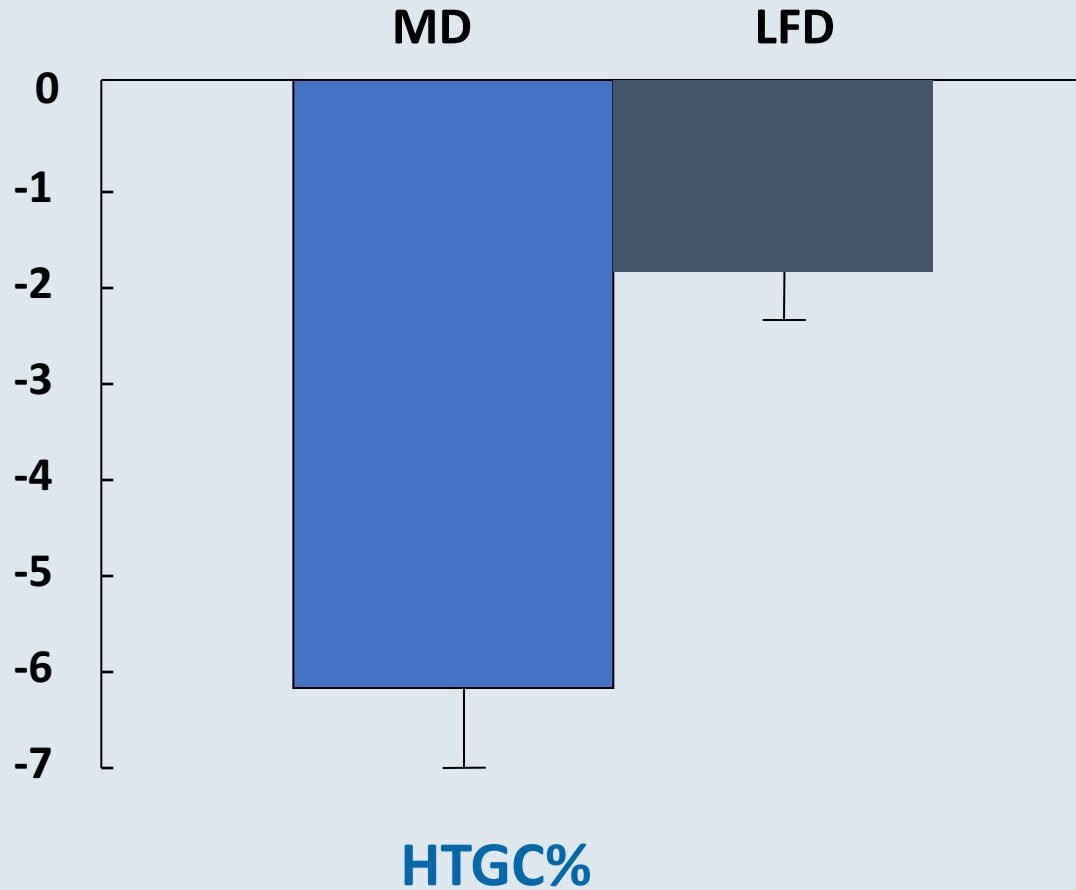
## Testing:

- Fasting laboratory samples
- 3-hour euglycemic clamp study
- MRI/MRS
- Diet education and provision of food

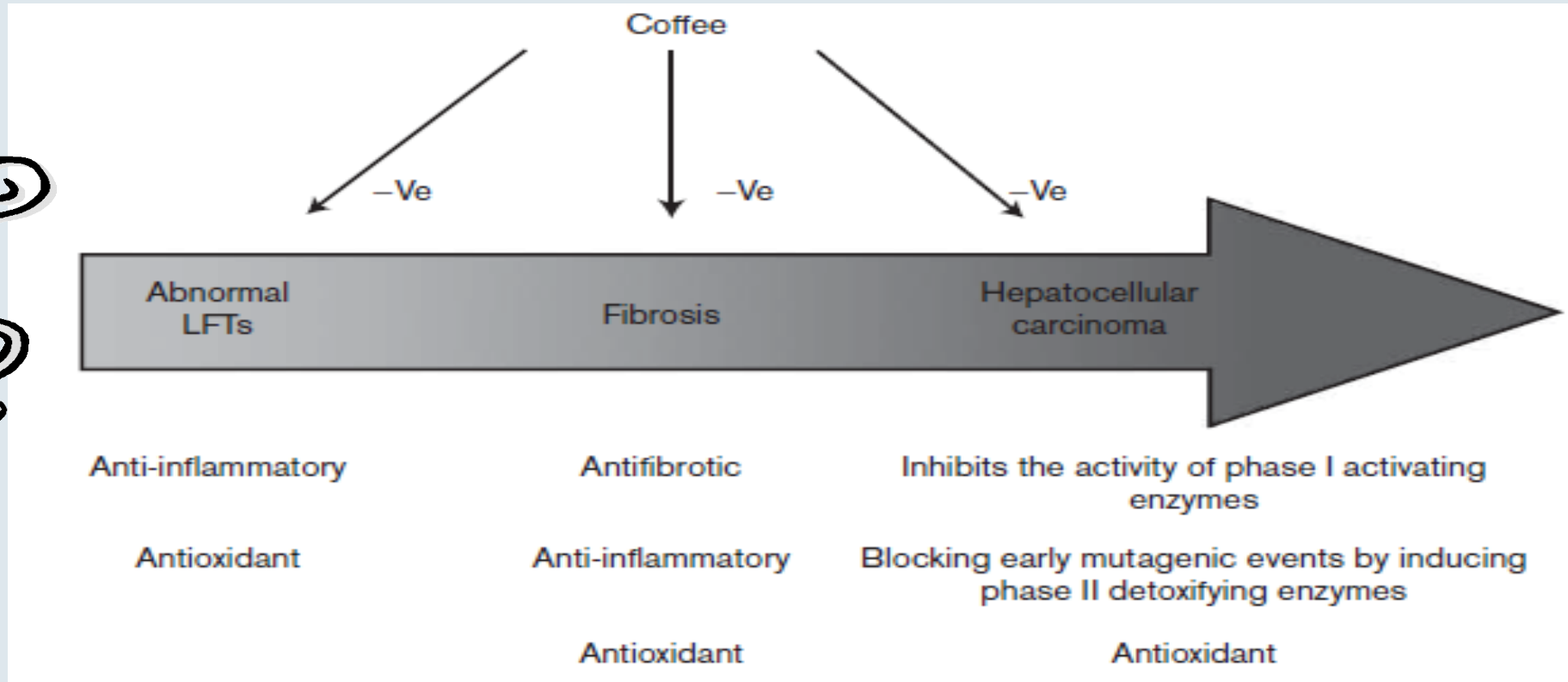
## Endpoints:

- Change in insulin sensitivity
- Change in hepatic steatosis

# Greater Reduction in Hepatic Fat and Greater Improvement in IS with MD than LFD



# Caffeine Intake is Protective Against NAFLD: Analysis of Population-Based Data from the US



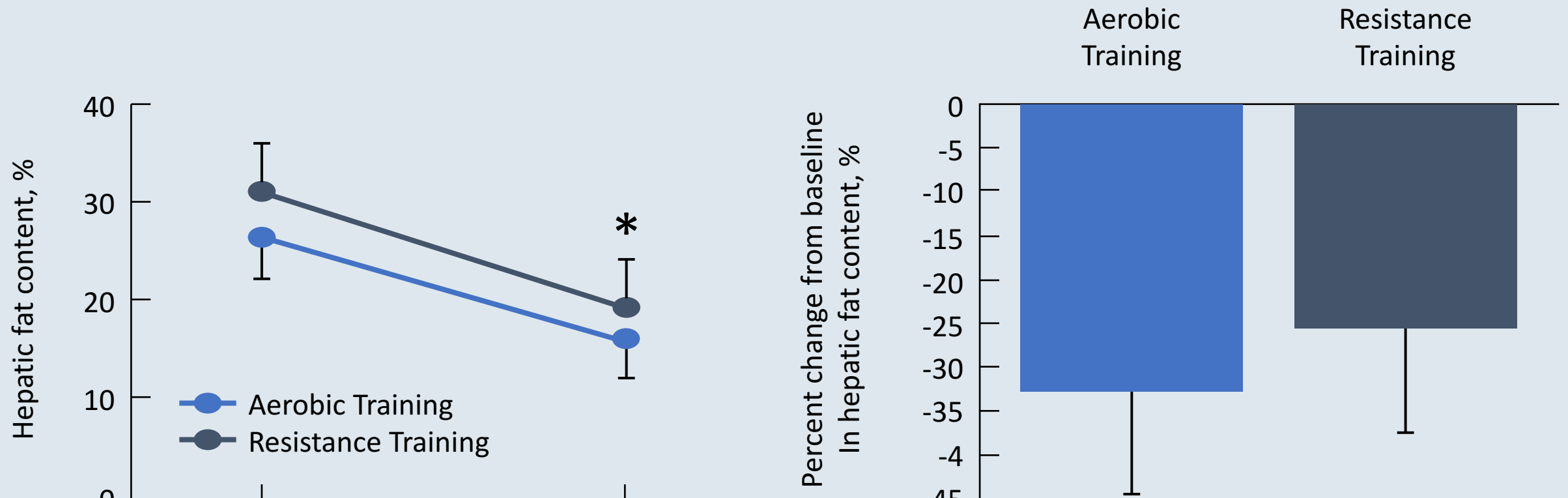
# Independent Predictors of NAFLD

Predictor	OR (95% CI)	P
African American Race	0.520 (0.426–0.633)	<0.0001
Male gender	1.329 (1.132–1.562)	0.0007
Obesity (BMI $\geq 30$ )	2.087 (1.808–2.409)	<0.0001
Caffeine (mg) intake	0.999319 (0.998955–0.999684)	0.0003
Total plain water consumed (g)	1.000065 (1.000008–1.000122)	0.0254

# Exercise: Aerobic or Resistance?



# Both Resistance Training and Aerobic Training Reduce Hepatic Fat Content



Moderate/ Vigorous Exercise: 30-45 min/day



# Changing the Attitude Toward Healthy Lifestyle in Texas



# The NAFLD Lifestyle





# Take Home Message

- NAFLD is very common and potentially serious liver disease even among children and young adults.
- **NASH-specific therapies** are coming soon and should change the attitude toward screening and treatment.
- Recommend coffee, Mediterranean diet, and exercise.